This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

Due to copyright issues, the study mentioned in this letter has been removed from the electronic version of this document. The study can be found in the paper version located in the OPP Public Regulatory Docket.

AMVAC

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June 30, 2000

Via Hand Delivery

Mr. Robert C. McNally, Chief (MC-7508W)
Special Review Branch
Special Review and Reregistration Division
United States Environmental
Protection Agency
1921 Jefferson Davis Highway
Crystal Mall 2
6th Floor
Arlington, VA 22202

Re: DDVP PRA

Dear Mr. McNally:

This letter is intended to supplement our previous correspondence regarding significant errors in the draft preliminary risk assessment (PRA) for dichlorvos dated April 15, 2000.[1/] It addresses critical errors in the "Short-Term Inhalation and Dermal" exposure scenario that is evaluated for several different exposure cases in the draft PRA.

More specifically, the toxicological endpoints that EPA cites based on the study it selected as the short-term endpoint for dermal and inhalation study -- decreased body weight and cholinergic signs at 2.5 mg/kg/day -- did not occur in the study. Because these effects did not occur in the study EPA cites, EPA cannot base its exposure scenarios on them. Moreover, if EPA were to use the rabbit study it cites, the NOAEL for 1-7 days exposure would be 2.5 mg/kg/day and the LOAEL would be 7.0 mg/kg/day based on clinical signs of treatment. There

1/ Amvac received this draft on April 24, 2000.

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are, however, strong reasons, discussed below, why this rabbit study is not acceptable for risk assessment purposes. Rather, these fundamental errors must be addressed before the draft PRA is released publicly.

DISCUSSION

The errors discussed in this letter affect the answer to two different issues that are key to PRA conclusions:

- What exposure scenarios for DDVP uses are appropriately described as "short-term"?
- What toxicology study and endpoint should be used for risk assessment purposes for "short-term" exposures to DDVP?

The draft PRA applies a "short-term" exposure scenario to a variety of very different DDVP exposure situations. While the phrase "short-term" is not defined in the PRA, the PRA references the June 10, 1999, Hazard Identification Assessment Review Committee (HIARC) memorandum entitled "Dichlorvos (DDVP) -- REPLACEMENT OF HUMAN STUDY USED IN RISK ASSESSMENTS -- Report of the Hazard Identification Assessment Review Committee" (HIARC, 1999). The HIARC document defines "short-term" as 1-7 days of exposure.[2/]

Amvac's previous submission, dated May 12, 2000, detailed errors regarding the usage scenarios for DDVP. It discussed, for example, the inappropriateness of describing residential spraying of a pressurized aerosol spray can as short-term exposure when clearly such an activity would not occur repeatedly for seven continuous days.

The toxicology study in animals that EPA selected for the "short-term" endpoint for dermal and inhalation toxicity is the developmental study in rabbits.[3/] The HIARC memorandum states the following in support of the short-term dermal and short-term inhalation toxicology endpoint:

2/ HIARC (1999) at 6.

3/ Tyl, R., Marr, M., and Myers, C. (1991). "Development Toxicity Evaluation of DDVP Administered by Gavage to New Zealand White Rabbits." Lab Project Number 60C-4629-30/40. Unpublished study prepared by Research Triangle Institute.

Dose and Endpoint for Risk Assessment: Maternal NOAEL = 0.1 mg/kg/day based on the cholinergic signs and decreases in body weight at 2.5 mg/kg/day.[4/]

This statement is a clear and significant error. The toxicological endpoints EPA cites are a decrease in body weight and clinical observations indicative of cholinergic signs at 2.5 mg/kg/day.[5/] The NOAEL listed by EPA is 0.1 mg/kg/day for 1-7 days of exposure. Neither an effect on body weight nor a treatment-related effect on clinical observations occurred in the study in the 2.5 mg/kg/day exposure group. EPA stated effects are not in agreement with the data contained in the study report. The report is clear that neither body weight nor clinical observations were affected in the 2.5 mg/kg/day dosage group. Further, the summary of the report from this study clearly indicates that neither of these effects occurred at 2.5 mg/kg/day. In animals in the group receiving 7.0 mg/kg/day, clinical signs associated with treatment were apparent. Body weight was not statistically affected by treatment at any dosage level.

More specifically, the report states the following:

- ***Body Weights:*** The abstract of the report of the study states on page 7: *"Maternal body weights and weight gains were statistically equivalent at all time points and intervals examined."* This is supported by the data in the report in Table 2, page 20.

Developmental Toxicity Evaluation of DDVP Administered by Gavage to New Zealand White Rabbits, Tyl, 1991

Maternal Body Weight gms.	DDVP Dosage mg/kg/day			
	0	0.1	2.5	7
Treatment day 1	3517	3398	3488	3524
Treatment day 3	3480	3433	3463	3477
Treatment day 6	3523	3458	3520	3531
Treatment day 9	3574	3523	3513	3579

4/ HIARC (1999) at 6.

5/ HIARC (1999) at 6.

(Data from Table 2, page 20.)

The data do not demonstrate any effect on maternal body weight during treatment and cannot be used to support an effect level on maternal body weight during 1-7 days of treatment with DDVP.

- ***Clinical Observations:*** The abstract of the report of the study states on page 8: *"Maternal clinical signs of toxicity were limited to doses at 7.0 mg/kg/day."* This is supported by the data in the report in Table 3, on page 23. EPA's HIARC document states that clinical signs of toxicity occurred during days 1-7 of treatment at 2.5 mg/kg/day.[6/] In the rabbit developmental study, days 1 to 7 of treatment occurred on gestational days 7 to 13. Table 3 of the study reports the following clinical observations noted during treatment days 1 to 7 in animals treated with 2.5 mg/kg/day of DDVP:

  Day 2 1 Animal with audible respiration. (Note: 1 control animal had labored breathing during the study.)

  Day 5 1 Animal was bleeding from the mouth due to a bite. (Note: this is not an effect from treatment.) 2 Animals had soft feces. (Note: 2 control animals had soft feces on the same day.)

  Day 6 1 Animal died. (Note: It is not possible to know whether this death was treatment related since no clinical signs or body weight changes indicative of treatment were apparent.)

There are no clinical signs that are treatment related in the 2.5 mg/kg/day dosage group reported in the study. If the rabbit developmental study by Tyl were used for risk assessment purposes, the NOAEL for 1-7 days exposure would be 2.5 mg/kg/day and the LOAEL would be 7.0 mg/kg/day based on clinical signs of treatment.

The toxicological endpoint selected by EPA from the rabbit developmental study by Tyl is not acceptable to use for risk assessment purposes for several reasons:

6/ HIARC (1999) at 6.

- Rabbits are extremely variable lot to lot and not consistent with respect to subchronic toxicity endpoints.

- Rabbits often have respiratory infections that result in sporadic deaths. When treated with a test substance, these infections may worsen. Interactive effects on morbidity and mortality may occur due to synergistic effects.

- The rabbit teratology study does not demonstrate any effect of DDVP on body weight or clinical observations in the 2.5 mg/kg/day dosage group from 1-7 days of treatment.

- The value EPA erroneously selected for the NOAEL from the Tyl study of 0.1 mg/kg/day is not in agreement with other short-term studies in either rats or rabbits that are available. The NOAEL for maternal toxicity supported by the data in the Tyl report for 1-7 days of exposure is 2.5 mg/kg/day, which is consistent with other developmental studies in rabbits and rats.

NOAELs from Developmental Toxicity Studies after Oral Administration of DDVP

Animal	Study	NOAEL mg/kg/day	Reference	Interpretation
Rabbit	Developmental	5	Schwetz, 1979[7/]	Investigator
Rat	Developmental	3	Tyl, 1991[8/]	Investigator
Rabbit	Developmental	2.5	Tyl, 1991[9/]	Investigator

7/ Schwetz, B.A., Ioset, H.D., Leong, B.K.J., and Staples, R.E. (1979). "Teratogenic Potential of Dichlorvos Given by Inhalation and Gavage to Mice and Rabbits." *Teratology* 20:383-387. A copy of this study is attached.

8/ Tyl, R., Marr, M., and Myers, C. (1991). "Developmental Toxicity Evaluation of DDVP Administered by Gavage to CD (Sprague-Dawley) Rats." Lab Project Number: 60C-4629-10/20. Unpublished study prepared by Research Triangle Institute.

9/ *See supra* note 3. EPA's interpretation of this study -- NOAEL of 0.1 mg/kg/day -- is not consistent with other available data.

* * * * *

Amvac urges EPA to address these critical errors before releasing the PRA publicly. We look forward to discussing this with you at your earliest opportunity.

Sincerely,

Ian S. Chart/ajm

Ian S. Chart
Director of Regulatory Affairs

cc: Mr. Jack E. Housenger (w/attachment)(via hand delivery)